CASE REPORT

Multiorgan failure associated with severe ovarian hyperstimulation syndrome due to inadequate protocol optimisation: a rare but avoidable complication

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SUMMARY

Ovarian hyperstimulation syndrome (OHSS) is a well-recognised iatrogenic complication following controlled ovarian stimulation (COS). Mild to moderate cases are mostly managed conservatively. Severe cases of OHSS can be potentially fatal. For this reason, UK clinics providing licensed fertility treatment are obliged to follow Human Fertilisation and Embryology Authority guidelines for reporting severe incidents. We present an unusually severe complication of OHSS resulting in significant morbidity. A nulligravida woman aged 25, with a 4-year history of subfertility and multiple risk factors for the development of OHSS, underwent COS. Immediately following oocyte retrieval, the patient developed symptoms of early-onset severe OHSS. The subsequent clinical deterioration of the patient precipitated multiple organ failure, including renal and hepatic dysfunction. Despite supportive management in an intensive care unit, the patient required transfer to a tertiary liver centre for specialist treatment. OHSS is a preventable complication; therefore, such an uncommon presentation of the syndrome provides important clinical lessons to be discussed.

BACKGROUND

It is important to establish a balance between sufficient ovarian stimulation to optimise pregnancy outcome, with minimising the risk of ovarian hyperstimulation syndrome (OHSS). This is achieved by selecting an appropriate protocol regime to stimulate the ovaries.¹ The purpose of presenting this case is, first, to remind clinicians of the importance of understanding the pathophysiology behind protocol regimes they initiate and the potential adverse clinical outcomes encroached on the patient when doing so; second, to highlight the need for a universal guideline for both the private and National Health Service (NHS) setting. Such guidance should take into consideration primary and secondary prevention measures and individualised protocol regimes to prevent the onset and severity of OHSS.

CASE PRESENTATION

A nulligravida woman aged 25, with a 4-year history of subfertility, was admitted to East Kent Hospital, following oocyte retrieval performed at a private

clinic. This patient had risk factors for the development of OHSS, such as a history of polycystic ovarian syndrome (PCOS) and raised anti-Müllerian hormone (50 pmol/L).

A short antagonist protocol was used to stimulate follicular growth by administering 150 units of Gonadotropin-releasing hormone (GnRH) for 13 days followed by one dose of human chorionic gonadotrophin hormone (hCG) to trigger ovulation 36 hours prior to oocyte retrieval despite multiple follicles (>25) seen on ultrasound. On the day of oocyte collection, the ovaries were observed to be severely hyperstimulated with evidence of ascites intra-abdominally. Nineteen oocytes were successfully collected, and the decision was made to freeze all embryos in an attempt to reduce the severity of hyperstimulation syndrome. No other supportive treatment was given within the private setting.

Immediately postoperatively, the patient presented with shortness of breath, vomiting, bilateral shoulder tip and pelvic pain. She was transferred to East Kent Hospital for further assessment. On admission to hospital, a pelvic ultrasound confirmed bilateral enlarged ovaries with the right measuring 14×11.6×7 cm and the left 13×7×6.6 cm. The following few days, she deteriorated with worsening features of OHSS, such as further enlargement of the ovaries 18×13×17 cm, up to 2 L of ascites and new onset bilateral pleural effusion. She demonstrated an acute renal failure with severe oliguria (<25 mL/hour), persistent dehydration and haemoconcentration despite adequate intravenous fluid resuscitation. She was transferred to the intensive care unit for supportive management.

By day 8 of admission, the hepatic enzymes increased sevenfold and clotting factors were deranged regardless of a normal liver ultrasound. Despite improvement of the clinical symptoms such as a reduction in ascites and corrected renal function managed on ITU, she required transfer to a tertiary liver centre 11 days after the oocyte collection for supportive management of her acute hepatic dysfunction.

TREATMENT

The principle of management was to maintain intravascular volume with a strict fluid balance

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and human albumin solution. This was successful in improving the renal function and ascites. Paracentesis was not deemed an appropriate treatment of ascites due to the risk of injury to other intra-abdominal organs given the size of the enlarged ovaries and also because of clotting abnormalities associated with hepatic dysfunction.

OUTCOME AND FOLLOW-UP

Following discharge from the tertiary liver centre, the patient was followed up 4 weeks following oocyte retrieval in our hospital fertility clinic. Liver function tests returned to normal baseline, an ultrasound scan reported normal ovarian size with no evidence of ascites and normal liver morphology.

DISCUSSION

OHSS is a recognised iatrogenic complication following COS to increase the number of oocytes available for assisted reproductive technology. The true incidence of OHSS remains unknown because there is no mandatory reporting for mild and moderate cases worldwide, although the incidence is reported to be between 3.1% and 8%.² The incidence of severe cases requiring hospitalisation within units must be reported accurately to the Human Fertilisation and Embryology Authority to aid patient safety.

There is no exact consensus for the cause of OHSS. However, it is believed that artificial stimulation of the ovaries and the use of exogenous hCG lead to the release of vasoactive proinflammatory mediators such as vascular endothelial growth factor (VEGF), prostaglandins and cytokines.² VEGF is thought to be the principle mediator for the clinical presentation of the syndrome. When VEGF binds to its corresponding receptor VEGFR-2, the resultant effect is an increased vascular permeability of the vessels.³ This causes endothelial injury and vasodilation, leading to a shift of fluid from the intravascular compartment to the third space.⁴ Third space fluid loss results in circulatory dysfunction manifesting as clinical signs of hypovolaemia, ascites, reduced renal perfusion and end-organ failure such as liver damage.⁵

The diagnosis of OHSS can be defined as early or late onset depending on the time of presentation from the trigger of the ovulation injection.⁶ Typically, early OHSS presents within 9 days of oocyte retrieval and reflects the effect of exogenous hCG on ovaries stimulated by gonadotropins.⁷ Late onset presents 10 days or more from oocyte retrieval and is likely to be related to the ovarian response to endogenous hCG derived from the trophoblast in early pregnancy.⁷ The risk of OHSS can be increased by certain pre-existing characteristics such as PCOS, a previous history of OHSS, increased antral follicle count or high levels of anti-Müllerian hormone.⁸

There are various prevention strategies to maintain the balance between sufficient stimulation of the ovary and reducing the risk of OHSS which will be discussed. Such strategies can be defined as primary or secondary measures. Primary prevention identifies the 'high-risk' patient and individualises protocols to prevent excessive ovarian response.⁶ Secondary prevention is aimed at patients who have expressed an excessive ovarian response to gonadotropin stimulation, with the goal to prevent progression to OHSS.¹

In a patient with PCOS, a lower dose of gonadotropin, such as 50–150 IU of follicle-stimulating hormone (FSH) is advised for follicular growth.⁴ The dose can be given in a 'step-up' or 'step-down' manner, whereby either a higher FSH dose is initiated then downtitrated or a lower dose is initiated and increased depending

on ovarian response.⁹ In this case, the patient was given 150 units of Gonal-F, which is invariably the higher range without any ovarian response monitoring to titrate the dose accordingly.

The use of metformin for the prevention of OHSS in patients with PCOS is also widely encouraged.¹⁰ Metformin inhibits the secretion of vasoactive mediators such as VEGF and thus reduces vascular permeability.¹¹ Evidence from a prospective randomised trial, in which all patients were given a low dose of stimulation (100 IU FSH) and metformin, showed a reduction in the incidence of severe OHSS from 20.4% to 3.8%.¹² Such significant findings reflect the importance of primary prevention measures on reducing the incidence of OHSS.

For many decades, gonadotropin-releasing hormone analogue (GnRH_a) triggering has been globally recognised as the most suitable approach for the stimulation of ovulation.¹³ Previously exogenous hCG was used to mimic the luteinising hormone (LH) surge in ovulation but was known to have a long half-life.¹⁴ Thus, it prolonged luteotropic effects and was associated with potentiating OHSS.¹⁵ GnRH_a stimulates the pituitary gland to produce an LH surge sufficient enough to trigger ovulation without the prolonged effects.¹⁶

Despite the universal use of GnRH_a, an unknown dose of hCG was given to trigger final oocyte maturation in this case, further potentiating risk for OHSS. If hCG should be used as part of a protocol regime, a lower dose of 5000 IU or less can be administered to initiate ovulation, but the embryos should be cryopreserved and transferred at a later date. This aims to avoid the outcome of imminent pregnancy, which would then increase the risk of late-onset OHSS.⁴

An effective secondary preventative measure is coasting which involves the withdrawal of the gonadotrophin used for final trigger of ovulation once a certain level of serum estradiol (E2) concentration (>15 000 pmol/L), or more than 20 follicles are present.¹⁷ Essentially, the use of hCG is delayed until E2 levels are decreased or plateaued to downregulate ovarian response, only then followed by oocyte retrieval and embryo transfer.⁶

An alternative prevention measure would be to consider in vitro oocyte maturation in high-risk patients with PCOS. Immature oocytes are retrieved from antral follicles prior to ovarian stimulation and subsequently matured in vitro before embryo

Learning points

- ▶ Severe OHSS is associated with mortality secondary to organ failure in which acute renal and hepatic dysfunction are recognised complications.
- ▶ It is essential clinicians understand the pathophysiology involved in artificial stimulation of the ovaries to prevent avoidable complications such as severe ovarian hyperstimulation syndrome (OHSS).
- ▶ A universal national guideline for the management of controlled ovarian stimulation should be considered to prevent such severe complications.
- ▶ Such guidance should consider primary prevention measures to reduce the onset of OHSS in high-risk patients, individualised protocol regimes and secondary prevention to reduce the severity in a patient who has expressed an excessive ovarian response to controlled ovarian stimulation.
- ▶ The most effective known regime for eliminating OHSS as supported by literature review is to trigger ovulation with a gonadotropin-releasing hormone analogue, followed by cryopreservation.

transfer.¹⁸ This remains a suggested strategy for female fertility preservation but at present not widely available on the NHS.

This case report is an example of inadequate optimisation of primary and secondary prevention measures to reduce the incidence of OHSS. Considering the individual risk factors, the most appropriate protocol regime was not administered, resulting in a very severe but avoidable presentation of OHSS. For many infertility patients, the reality of multiple IVF cycles to achieve pregnancy is a prospect. Considering the physical and psychological impact, it is our responsibility as clinicians to ensure adequate balance between sufficient ovarian stimulation and risk of OHSS. This is an achievable outcome considering literature review supports evidence for reduced incidences of OHSS associated with tailored protocol regimes. There is a clear need therefore, for further guidance from our national regulating body which should consider current evidence, incorporation of primary and secondary prevention measures and individualised protocol regimes to eliminate OHSS from practice.

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